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Multiple drug allergies: Recommendations for perioperative management

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Life-threatening hypersensitivity reactions are more likely to occur in patients with a history of allergy, atopy, or asthma. Hence, in a patient who presented with a history of multiple drug allergies (MDA), an allergological assessment should be performed prior to surgical procedure. Drug allergies, being one of the causes of

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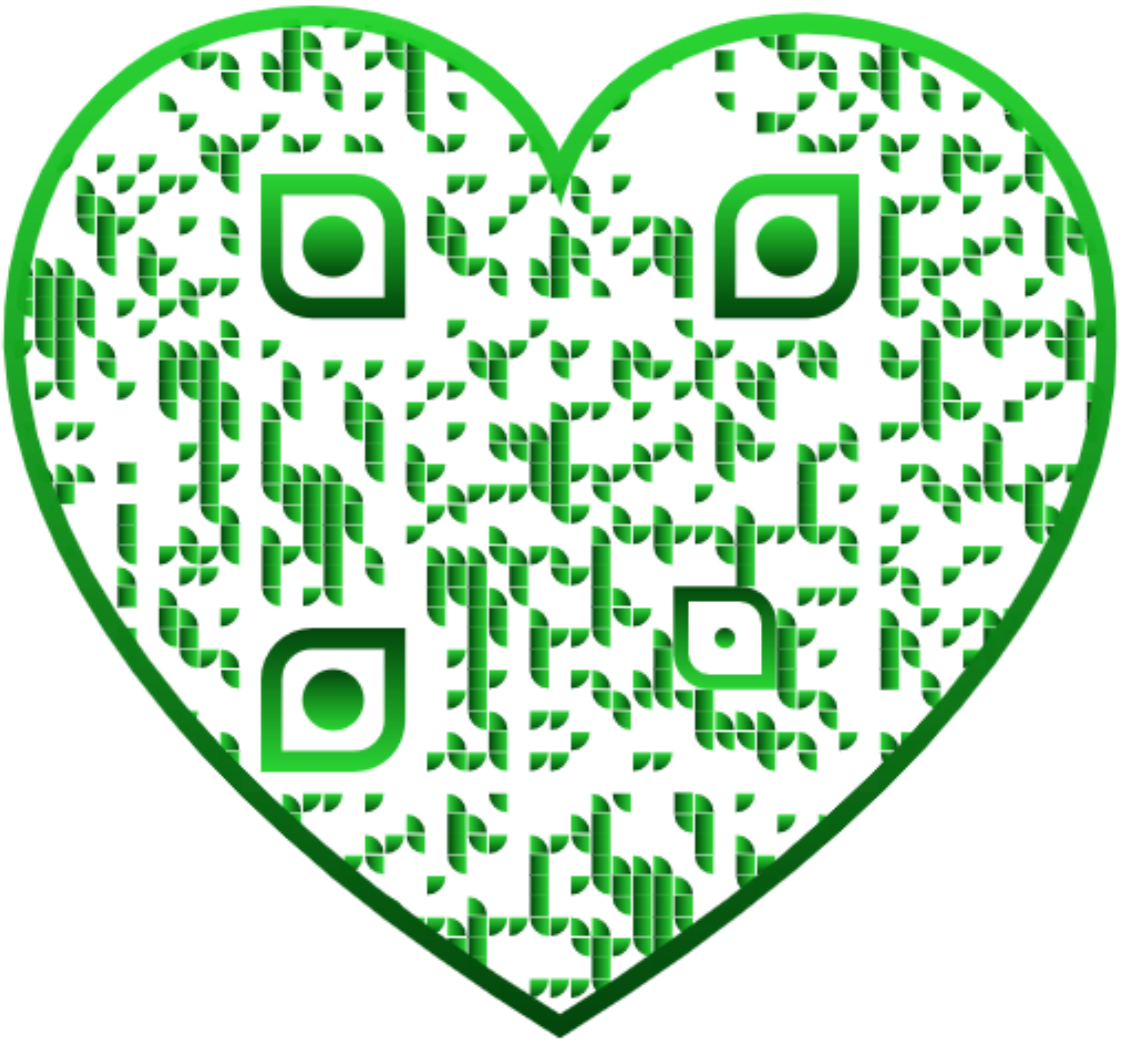

catastrophic events occurring in the perioperative period, are of major concern to anesthesiologists. Neuromuscular blocking agents are regularly used during anesthesia and are one of the most common causes of perioperative anaphylaxis. They are estimated to be responsible for 50%–70% of perioperative hypersensitivity reactions. Antibiotics and latex represent the next two groups of drug allergy. Allergic reactions to propofol are rare with an incidence of 1:60,000 exposures. Although intraoperative drug anaphylaxis is rare, it contributes to 4.3% of deaths occurring during general anesthesia. These recommendations discuss pathophysiology of MDA, preoperative evaluation, and anesthesia considerations as well as the prevention and management of allergic reactions in anesthetized patients with a history of MDA.
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Introduction

Drug hypersensitivity is a general term to describe the onset of objective symptoms in response to a medication at certain doses that typically do not cause adverse effects in non-hypersensitive patients. It refers to both drug allergy and pseudoallergic reactions. Drug allergy is an immunological reaction elicited by medications. It is commonly divided into four categories based on the cellular and molecular mechanisms of pathogenesis. 1) Type 1 allergy is an immediate reaction mediated by IgE activation on mast cells and basophils, 2) Type 2 allergy is a delayed reaction related to IgG-mediated cell destruction, 3) Type 3 reaction is mediated by the IgG-drug complex and the activation of complement systems, and 4) Type 4 reaction has a delayed onset caused by T cell activation. Type 4 reaction has been considered as the most prevalent type of reaction. One of the fatal examples of Type 4 reaction is toxic epidermal necrolysis (TEN), in which CD8+ T cells are activated and cause cell destruction mainly through granulysin [1]. While potentially lethal, drug allergy is relatively uncommon. The prevalence of drug allergy varies depending on the specific medication. For example, penicillin allergy is the most reported drug allergy, and up to 10% of all patients reported some degree of penicillin allergy. It was estimated that drug allergy occurs in 1–2% of all admitted patients, and in 3–5% of hospitalized patients [2]. However, the overall prevalence of drug allergy is hard to measure. This is because many patients are not aware of their existing drug allergy, while some others were misdiagnosed with allergy to certain drugs in their childhood and carry the label into their adulthood. Risk factors of drug allergy include drug factors and host factors. Penicillin, aspirin, and sulfonamides account for about 80% of allergic reactions, however, it is difficult to predict sensitization based on the chemical structure of drugs. Most allergic reactions appear in the first few weeks of therapy, and intermittent administration at moderate doses poses higher risk than long-term usage of the drug [3]. It was suggested that the route of administration may also play a role, and risk follows the order of topical > oral > intravenous (IV), although the likelihood of deadly anaphylaxis is higher with the IV route [4]. In terms of host risk factors, female sex, genetic factors, previous drug allergy, and current disease situation should be taken into consideration [5,6]. Patients who are allergic to one drug often demonstrate reactions to other medications with similar chemical structure (e.g., penicillin and cephalosporin); however, sometimes patients may develop immunological reactions to chemically unrelated drugs, which is referred to as multiple drug allergies (MDA). One direct explanation of MDA is enhanced responsiveness of patient's eosinophils and T cells upon the administration of a previous drug [7]. As the sensitization fails to subside, patients become abnormally sensitive to non-cross-reacting drugs. Patients with MDA need to be carefully evaluated for surgical procedures, as perioperative drug allergies may cause catastrophic events including death. Therefore, in the present investigation, pathophysiology of MDA, preoperative evaluation, and anesthesia in patients with MDA, and prevention and management of allergic reactions in anesthetized patients are discussed.

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Pathophysiology of multiple drug allergies

A fundamental principle behind all immunological adverse reactions, whether induced by a medication or another stimulus, is the misalignment of an individual's host immune defenses against at least one type of molecule that is not perceived to be antigenic in the general population. Each pathological response to such misalignment generally requires an interaction between an individual having an applicable genetic predilection and specific environmental exposure; in the absence of either component, clinical symptoms typically will not occur.

Drug reactions are well-described by the Gell and Coombs classification of hypersensitivity reactions; this classification details commonalities between different types of adverse immune responses based on their cellular mechanisms and is independent of clinical manifestations. Under the Gell and Coombs classification, Type I, II, and III hypersensitivity reactions are mediated through a humoral immune response, whereas Type IV hypersensitivity reactions are cell-mediated responses. All hypersensitivity reactions require a sensitization period wherein there is a lag between an individual's initial exposure to an antigenic compound and the generation of an immunological response. Clinical manifestations will only theoretically develop following a subsequent exposure. The pathophysiology of each type of hypersensitivity is described in detail below (See Table 1).

Type I reactions

Type I hypersensitivity reactions are colloquially regarded as “classic” allergic reactions. These types of reactions are characterized by their biphasic onset on action. Additionally, Type I hypersensitivity reactions are unique in that the sensitization period leads to the development of a robust IgE response that produced B-lymphocytes through the influence of interleukin-4 and T-helper type 2 cells.

The composition of IgE response promotes the mechanism of the immediate portion of the biphasic reaction. IgE, a monomer, contains a constant region (Fc), a structure that allows this molecule to be anchored to effector cells. This region binds to the Fc receptor on the cell membrane of mast cells and basophils. Opposite to the constant region on the IgE molecule are variable regions; these regions are exposed to extracellular spaces and recognize the specific allergenic peptide sequences or epitopes. A single antigen must be recognized by two cytophilic (bound) IgE molecules and lead to their cross-linking. This in turn causes the rapid degranulation of preformed proinflammatory compounds, namely histamine, neutrophil and eosinophil chemotaxis factors, and proteolytic enzymes. These mediators [alongside the histological location of the effector cells] are responsible for many of the clinical symptoms observed with regard to allergic reactions. For example, the degranulation of mast cells/basophils in the skin leads to localized vasodilation and pruritus observed as urticaria or hives. Similarly, vasodilation and increased vascular permeability of the airways lead to edema/bronchoconstriction, and thus shortness of breath/air trapping. Anaphylaxis occurs when the effects of an allergic reaction are apparent in two different organ systems, with the most common symptom being hypotension.

The delayed phase of Type I hypersensitivity reactions peak 6–12 h after immediate-phase response. As noted above, the immediate-phase response's proinflammatory mediators promote histological changes that allow for the infiltration and recruitment of new immune effector cells. Thus, the delayed-phase response is denoted by the presence and activation of neutrophils, eosinophils, and macrophages [by the gradual release of arachidonic acid metabolites: prostaglandins and leukotriene alongside the stimulation of the kinin system], and the subsequent destruction of surrounding epithelial tissue. Recurrent exposure to allergens leads to a chronic inflammatory state observed in atopic diseases like asthma; however, in the setting to drug reactions, the delayed-phase of type I hypersensitivity reactions is likely less contributory [8].

Type II reactions

Type II hypersensitivity reactions are characterized by their cytotoxic effects. This type of pathological response involves the development of a novel antigenic compound generated by the interaction of exogenous substances (i.e., medication) and a host's own cellular components. These small

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Table 1
Classification of drug reactions.

	Mechanism	Common Manifestations (not inclusive)	Common Drugs Implicated (not inclusive)
Type I Hypersensitivity	Immediate: Crosslinking of cytophilic IgE- mediated rapid degranulation of mast cells and basophils (triggers the release of histamine, etc.) Delayed: Local infiltration of neutrophils, eosinophils, and macrophages through slow release of proinflammatory prostaglandins and leukotrienes	Urticaria, acute asthma exacerbation, angioedema, and anaphylaxis Chronic atopic disease (i.e., asthma and eczema)	B-lactams, sulfonamides, insulin, lidocaine, contrast media, and aspirin [11] Less contributory due to lack of chronic exposure (as opposed to environmental elements)
Type II Hypersensitivity	Cytotoxicity: Haptenization of immunogen and cellular component IgG or IgM-mediated opsonization and/or complement fixation (formation of membrane attack complex leading to cell lysis)	Cutaneous manifestations: drug-induced pemphigus, thrombocytopenia purpura Hemolytic anemia	Allopurinol, ampicillin, aspirin, glucocorticoids, sulfonamide, sulfa, diuretics, NSAIDs, carbamazepine, and hydantoins [4] Sulfonamides, Beta-lactams, methyldopa, levodopa, quinidine, procainamide, antituberculous meds [4]
Type III Hypersensitivity	Soluble IgG or IgM complexed to soluble antigen accumulation in postcapillary venules	Drug-induced vasculitis Serum-sickness	Allopurinol, sulfonamides, thiazides, and penicillin [4] Aspirin, PTU, sulfonamides, penicillins, Equine serum, chimeric biologics (i.e., rituximab and infliximab), and exogenous human immunoglobulins [4]
Type IV Hypersensitivity	Cellular necrosis of antigen presenting haptenized cells by cytotoxic [CD8+] T cells	Fixed-drug eruptions Steven-Johnson's Syndrome/ Toxic epidermal necrolysis	Phenytoin, carbamazepine, methyldopa, barbiturates, salicylates, and sulfonamides tetracycline, thiazides [4]
Non- Immunological Reactions	Various (i.e., therapeutic mechanisms of medication, accumulation of medication or metabolites, and mechanism not yet defined)	Various across all organ systems	E-mycin leading to diarrhea Topical 5′FU leading to surrounding skin necrosis Chronic transfusion dependence leading to secondary hemochromatosis (hepatic dysfunction) Copper IUD leading to exacerbations in Wilson's disease (Parkinsonism syndrome) [5]

molecular weight peptides, known as haptens, are rigidly fixed to a cell's surface through covalent bonding. These immunogenic compounds lead to the formation of IgM or IgG autoantibodies against a host's cellular components or extracellular matrix. IgG, a monomer, is the most abundant immunoglobulin in the body and found largely in the serum and interstitial fluid. IgM, a pentamer, is limited to the intravascular compartment by its large size. Both compounds allow for the direct recognition and destruction of the antigenic material by neutrophils and macrophages through opsonization (phagocytosis) or exocytosis of digestive enzymes. Additionally, the constant regions of these immunoglobulins have the unique ability to stabilize the complement pathway; this nonantigen-specific immune response amplifies the ability of neutrophils, macrophages, and natural killer cells to neutralize foreign

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compounds while creating membrane attack complexes, porous formations that facilitate cell lysis [8]. These reactions affect nearly every organ system; however, cutaneous manifestations (i.e., drug-induced pemphigus and thrombocytopenia purpura) and hemolytic anemia are mostly related to drug reactions. Common drug culprits giving rise to Type II reactions include beta-lactams, sulfonamides, isoniazid, antiepileptics, and quinidine [9].

Type III reactions

Type III hypersensitivity reactions are characterized by the accumulation of immunocomplexes. These mediators consist of a soluble antigen coupled to soluble IgG or IgM that deposit in either a localized or systemic fashion. These compounds have a predilection to collect in postcapillary venules. Organ systems with a rich vascular supply (i.e., kidneys, skin, joints, and lungs) are preferentially affected. These immunocomplexes trigger cellular damage by the same mechanisms as type II hypersensitivity reactions (i.e., opsonization and complement fixation) alongside platelet activation, prompting thrombus generation [8]. Manifestations of type III hypersensitivity reactions include drug-induced vasculitis and serum or serum-like sickness. The symptoms of drug-induced vasculitis maybe limited to the skin (i.e., palpable purpura) or cause end-organ damage, namely pulmonary hemorrhage or glomerulonephritis that is seen with other systemic small-vessel vasculitides. Drug-induced vasculitis may occur following the administration of sulfonamides, allopurinol, thiazides, or penicillins. Serum and serum-like sickness are denoted by the presence of fever, arthritis, and urticaria at ~10 days following secondary exposure to an "heterologous serum or another protein drug," namely chimeric biologics/pooled donor immunoglobulins, or penicillins/sulfonamides/aspirin, respectively [10,11].

Type IV reactions

Type IV hypersensitivity reactions are characterized by their delayed onset of action. Here, clinical symptoms are observed between 24 and 72 h after the initial exposure to an antigen. It is important to note that this interval is different from the sensitization period seen with the other hypersensitivity reactions. Though not unique to this type of hypersensitivity reaction, Type IV hypersensitivity reactions involve the generation of new antigenic compounds through the hapten model previously described. However, these pathological responses differ from other hypersensitivity reactions in that they are T-cell specific immune responses. This distinct mechanism occurs by "the inappropriate activation of cytotoxic T-cells [CD8+] that induce necrosis of antigen-presenting cells [through the liberation of cytokines]" and is distinguished by "a marked lymphocytic infiltration on histologic evaluation"; there is limited involvement of any immunoglobulins [12]. The most common manifestation of Type IV hypersensitivity reactions are contact dermatitis and fixed drug eruptions. Although contact dermatitis may occur with topical medications, such as antimicrobials or anesthetics, dermatitis is more likely the result of reactions to additives included in the topical formulation. Fixed drug eruptions are denoted by the development of "a solitary round or ovoid, erythematous, bright red or dusky red macules that may evolve into an edematous plaque" and result in a single area of hyperpigmentation upon drug withdrawal; these reactions are relatively benign and are associated with barbiturates, phenytoin, and sulfonamide exposure [9]. However, some life-threating systemic drug reactions, such as Steven Johnson's Syndrome and TEN, are explained by Type IV hypersensitivity mechanism. Here, different polymorphisms of the human leukocyte antigen class I molecules, compounds that present antigens to cytotoxic T-cells, have the propensity to interact with drug immunogens to cause widespread inflammation and epithelial necrosis. Drug responses implicated by this mechanism include reactions to phenytoin, carbamazepine, and allopurinol [11,12].

It is important to designate other drug intolerances that exist and which do not abide by mechanisms denoted above; such intolerances are known as non-immunological hypersensitivities. This catch-all term encompasses many different processes responsible for given intolerances, including those attributed to the therapeutic properties of a medicine, those that caused accumulations of the drug or metabolites explained by either an enzymatic defect or dose-dependent administration, or those where a finite cellular process has yet to be defined. A well-known example is the association

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between erythromycin and diarrhea; erythromycin, a macrolide antibiotic, agonizes motilin and activates gut peristalsis, which accounts for the drug's laxative properties. Similarly, hepatic dysfunction may develop in individuals with acquired hemochromatosis secondary to chronic transfusion requirements [12]. Whatever the case, the importance of a detailed drug allergy history cannot be overemphasized; the categorization of different intolerances or hypersensitivities can be used to either triage the severity of a given reaction and identify if certain therapies can treat a reaction's manifestations or mitigate side effects. It is important that clinicians weigh benefits and risks of any drug prior to administration and participate in shared decision-making with their patients to promote autonomy and greater adherence to therapy.

Preoperative evaluation

Perioperative allergic reactions range from minor to life-threatening in severity, and serve as a major source of concern for anesthesiologists and the entire perioperative care team [13]. Prevention of such occurrences is centered on the identification of patients at risk. It has been well-demonstrated that the most crucial preventative strategy is a thorough clinical history upon initial preoperative evaluation [13,14]. Anesthesiologists should investigate clinical history of allergy or perioperative allergic reactions, and all previous medical conditions and their treatments [14]. In estimating the risk of allergic reactions, factors of concern are multiple surgical procedures, history of asthma or atopy, and advanced age [15,16]. Female gender and frequent prescription of antibiotics for short term use are other well-documented risk factors for perioperative hypersensitivity [16–18]. Along with female gender, a large-scale retrospective study showed significantly higher rates of MDA diagnoses associated with prior hospital admissions and the presence of comorbidities [16]. Similarly, there was a positive correlation between the number of comorbidities and percent of MDA diagnoses [16]. These findings are depicted in Fig. 1.

Following clinical history, it is essential that appropriate steps are taken toward the evaluation and management of risk factors discovered. In patients found to be at risk for perioperative hypersensitivity or those having an unclear history of allergic reaction, it is recommended that a referral is made for thorough allergological evaluation to identify all potentially offending agents [13,14]. The examination should also be done following unforeseen hypersensitivity events to prevent their occurrence in the future. Allergological evaluation, when used together with clinical history and physical examination is the most promising strategy for the accurate diagnosis of hypersensitivity reaction [20].The components of the evaluation are determined based on individual risk factors and the nature of previous allergic reactions. Specifically, investigative tests are chosen depending on whether a reaction is IgE or non-IgE mediated [14,21].

In vitro tests

In vitro tests are performed during the acute phase of a reaction or hours after the reaction has subsided [14]. Some examples of in vitro tests are serum total tryptase levels, allergen-specific IgE levels, CAST-enzyme linked immunosorbent assay (ELIZA), and lymphocyte transformation tests (LTTs) [14].

Serum total tryptase levels

Serum tryptase levels are helpful in diagnoses of anaphylaxis. A true IgE-mediated anaphylactic reaction is identified by the elevation of serum tryptase levels within 1–2 h of the event [14,20]. Elevated baseline tryptase levels have been well-documented to correlate with anaphylactic reactions of increased severity [22]. Despite its usefulness, this test is expensive. Additionally, prior evidence has indicated normal measurements of serum tryptase in some cases of potentially fatal anaphylactic episodes [19,23].

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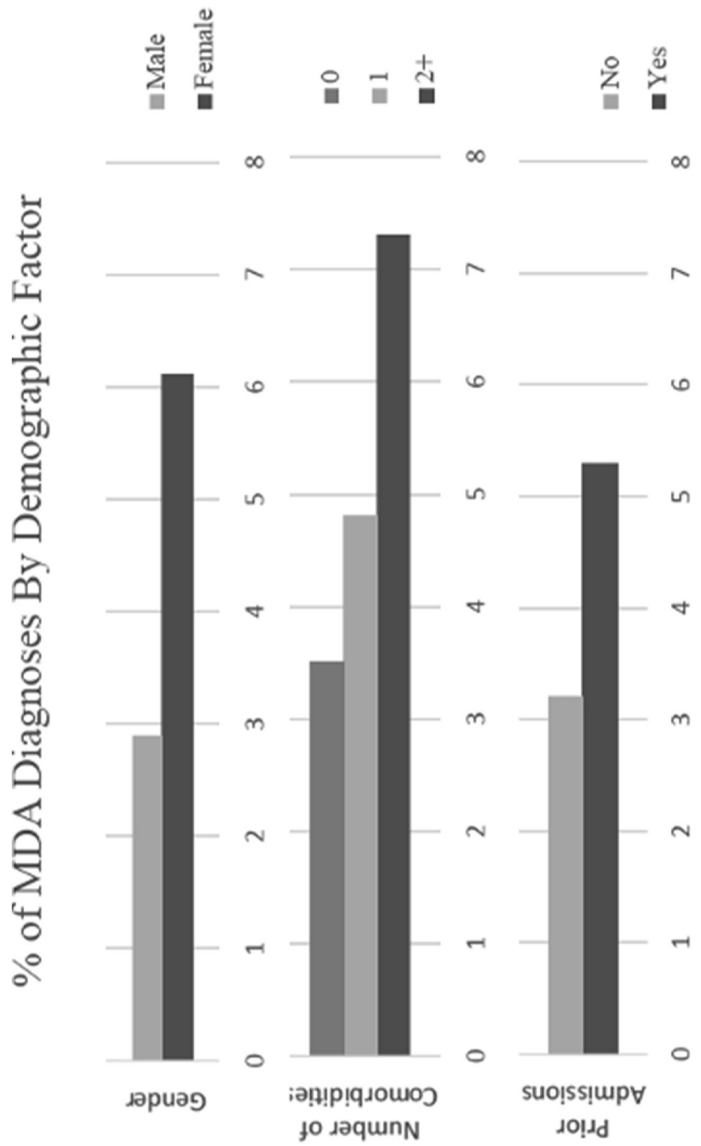

Fig. 1. Percent of MDA diagnoses by Demographic factor. Efficient risk stratification allows the early execution of preventative measures, so that complications are minimized in the perioperative period. The patient's role in hypersensitivity prevention has also been emphasized. Education of patients and their family members with respect to their current medications and possible cross-reacting agents may aid considerably in initial preoperative evaluation [19] (this figure is an original work by the authors). MDA, multiple drug allergies; MDH, multiple drug hypersensitivity.

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Allergen-specific IgE levels

Evaluation of allergen-specific IgE levels is beneficial when interpreted in combination with skin test results, but not alone [14]. This test has high specificity for the offending agent tested. Allergen-specific IgE tests are commercially available in clinical practice for a limited variety of drugs as ImmunoCAP fluorescent enzyme immunoassay [13,19]. These tests are known to be useful only in the resolution phase of allergic reactions. It has been demonstrated that IgE levels lack clinical utility as a preoperative screening tool for the risk of allergic reaction, even in patients with a history of atopy or drug allergy [13].

CAST-enzyme linked immunosorbent assay

Although less commonly utilized, the CAST-ELISA is considered to be an in vitro allergy provocation test [19,24]. This test detects sulfidoleukotriene synthesis by the patient's collected blood leukocyte fraction upon exposure to the allergen of interest [19,24].

Lymphocyte transformation test

LTT is most useful in the identification of type 4 (T-cell mediated) hypersensitivity reactions for numerous types of drugs [19,24]. This test is specific to drug and reaction type, although a negative test cannot exclude the presence of a hypersensitivity reaction [19,24].

In vivo tests

Commonly performed in vivo tests include skin prick tests (SPTs), intradermal tests, skin patch tests, and drug challenge (also known as drug provocation) tests.

Skin prick test

The identification of IgE-mediated hypersensitivity can be achieved by the utilization of SPTs [14,25]. In patients with previous history of allergy, it is mandatory that SPTs be performed for all agents necessary for anesthesia, including a muscle relaxant and an opioid derivative [14]. Antihistamine or corticosteroid medications should be temporarily stopped prior to performing the test to ensure accurate results [15]. SPTs are defined as positive in the presence of a mean wheal diameter of >3 mm produced in response to allergens [25,26]. Positive SPTs should be followed by an intradermal test (IDT) in the same location on the skin, particularly in those at higher risk of anaphylactic episodes [14,25,27].

Intradermal tests

IDT involves injecting a small amount of allergen under the skin, followed by the measurement of wheal diameter after 15–20 min, or between 24 and 72 h if evaluating a delayed hypersensitivity reaction [25]. If the wheal has increased by > 3 mm compared to baseline diameter of the initial wheal made by the SPT, then the test is defined as positive [25,26]. The IDT is more sensitive than the SPT, but is associated with higher risk of IgE-mediated anaphylaxis and false positives [25].

Skin patch tests

The skin patch test is useful in the diagnosis of delayed-type hypersensitivity reactions. The test involves imbedding the allergen of interest onto a patch and placing it on the skin. Results are read after 1 day and then after 2–3 days, in which case the patch can be removed [27].

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Drug provocation tests

Drug provocation tests (DPTs) are considered the gold standard in diagnosing drug hypersensitivity reactions [14]. DPTs involve administering slowly increasing dosages of the drug of interest at equal time intervals, until the reaction occurs or until the therapeutic dose is reached [14,28,29]. DPTs are intended to objectively reproduce hypersensitivity symptoms in a well-controlled environment, where strict supervision with highly trained professionals is suggested [14,28,29]. Because of the potential to produce severe hypersensitivity reaction, DPT should be avoided in elderly patients, those with comorbidities, pregnancy, uncontrolled asthma, infection, severe drug hypersensitivity, or other circumstances that may prevent the adequate control of the reaction produced [28,29]. A DPT should be considered to investigate safe alternatives to currently offending agents and to diagnose a drug allergy when clinical history of the reaction is ambiguous and other allergological tests are unclear or unavailable [28,29] For drugs administered in the surgery area, an analysis weighing risks and benefits should be performed, and informed consent should be obtained prior to performing the DPT [28–31].

After allergological examination

Following the completion of diagnostic tests, a medical report must be produced, which provides risk factors gathered from clinical history, details on the offending drugs tested, results of allergological tests performed, and new diagnoses along with recommendations for future patient management [14]. If hypersensitivity reactions were produced during testing (such as a DPT) or unforeseen reactions are being reported, documentation should include potential offending agents administered, time of administration, signs and symptoms of the resultant hypersensitivity reaction, the grade of severity, the drugs administered which successfully treated the reaction and the time required for symptoms to resolve [14,20]. This is particularly important in guiding future preventative measures for perioperative allergic reactions. Previously uninvestigated hypersensitivity events during the perioperative period are a well-documented risk factor for life-threatening allergic reactions in the future [20]. Detailed documentation combined with clinical history and allergological examination plays a crucial role in the identification of drug allergy and guiding decision-making with regard to anesthetic procedures in the future [14].

Cross reactivity and hypersensitivity risk

In patients with a history of allergy, potentially cross-reactive drugs and foods are commonly considered a contributing factor to the risk of perioperative hypersensitivity events [2,20]. Allergic cross-reactivity describes a phenomenon in which multiple allergens with structurally or chemically similar epitopes are recognized by the same antibodies, and elicit an allergic response in an individual without the need for direct exposure to more than one cross-reactive allergen [32]. The concept of cross-reactivity may provide the explanation for allergic reactions in patients receiving a drug for the first time [33]. Cross-reactivity can be created by similarities as small-scale as primary amino acid sequence, to those beyond the intrinsic characteristics of the epitope itself, such as protein glycosylation patterns [32,34]. Cross-reactivity has been frequently delineated with neuromuscular blocking agents (NMBAs), antibiotics, iodinated contrast agents, and specific foods [20]. In clinical practice, frequent misconceptions of cross-reactivity between certain drugs and foods result in the unvalidated attribution of risk toward hypersensitivity events and subsequent avoidance in patients reporting a history of allergy [20]. For example, concerns of cross-reactivity between penicillin and cephalosporins have led to the avoidance of cephalosporins in patients with reported penicillin allergy. The studies first investigating cross-reactivity between these two drug classes were published 50 and 60 years ago and incorrectly indicated the shared beta-lactam ring structure as the culprit [35,36]. More recent studies indicated that similarities in the variable R1 side chain, not the beta-lactam ring, are responsible for allergic cross-reactivity between penicillins and cephalosporins [37,38]. It is now predicted that only 1% of patients will have an allergy to a penicillin and cephalosporin that do not share similarities in the R1 side chain [39]. Thus, the assumption of cross-reactivity between these drugs and consequent avoidance is inconsistent with current data.

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Approaches to patients' anesthetic plans are complicated by unvalidated considerations of food allergies as contraindications to certain medications [20]. For example, the use of propofol is frequently avoided in patients with egg allergy. Yet, it is now known that the component used in propofol (an egg yolk lecithin) is not the allergenic component of eggs [40]. This was later confirmed by negative SPTs in response to both egg lecithin and propofol in pediatric patients with reported egg allergies [20]. This finding emphasizes the importance of confirming cross-reactivity with appropriate allergological tests. Other frequently avoided food and drug pairs that have been contradicted by recent evidence are soy or peanut allergy and propofol, shellfish allergy and iodinated contrast media, and fish allergy and protamine sulfate [20]. Misconceptions of cross-reactivity present more challenges to anesthesiologists, but also have considerable impact on patient outcomes—even when hypersensitivity reactions are avoided. For example, cefazolin is an intraoperatively used cephalosporin that is associated with fewer allergic reactions and adverse effects [41–43]. A study investigating more than 9000 surgical procedures found a higher risk of surgical site infections in patients not given cefazolin (a beneficial intraoperative cephalosporin), in an attempt to avoid allergic reaction in those reporting penicillin allergies [19,44].

To mitigate such complications, it is recommended that allergies and potential cross-reactive agents be confirmed with appropriate allergological tests, usually SPTs [13,14,20]. Cephalosporins that produced a negative SPT did not produce an allergic reaction in DPT when given to patients with penicillin allergies [13]. Despite the usefulness of SPTs, anesthesiologists should approach cross-reactivity diagnoses with caution. Previous evidence demonstrated that some penicillins produced a positive reaction to drug challenge in patients with penicillin allergies, despite producing negative SPTs [13]. Maintaining the knowledge of all cross-reactive drugs, including those which create these discrepancies is essential in the prevention of perioperative hypersensitivity. This is particularly important in emergent situations, which present challenges in the ability to perform such tests. It is recommended in these circumstances that all cross-reactive agents be avoided in patients with available previous record of allergy [13].

Multiple drug allergy syndrome vs. cross-reactivity

Misperceptions of cross-reactivity potentially lead to unfounded diagnoses of multiple drug allergy, contributing to further complication in the management of patients with a history of allergic reactions [20]. Multiple drug allergies, also known as multiple drug hypersensitivity syndrome (MDH), is considered a major risk factor for hypersensitivity events in the perioperative period [20]. MDH is defined as the propensity to produce allergic reactions toward 2 or more chemically unrelated agents, where these reactions have been confirmed by skin tests or in vitro tests [45–47]. This is in contrast to cross-reactivity, where reactions are provoked to drugs sharing chemical or structural similarity. Risk factors for MDH are the same as those for perioperative hypersensitivity, such as increased age, comorbidities, prior hospital admissions, and female gender [16]. Numerous patients report "multiple drug allergies" during initial preoperative evaluation, despite the majority of these allergies lacking appropriate confirmation [20]. In a meta-analysis of 24 studies, over 95% of patients considered allergic to penicillin were determined to have a negative skin prick test to penicillin and no IgE-mediated penicillin allergy [48]. It is now known that the majority of self-reported penicillin allergies are incorrect. Additionally, evidence has demonstrated instances in which insufficient investigation of prior allergic reactions caused misconceptions on the specific etiology of the reaction [49,50]. Such circumstances contribute to incorrectly confirmed allergies and rising numbers of unfounded MDA diagnoses. For these reasons, it is crucial that diagnoses of MDH be confirmed by positive skin tests or in vitro tests [46,47]. Taking such measures can mitigate the frequency of incorrect diagnoses of MDH, lower the risk of future allergic reactions, and ease the complexity of perioperative management in patients with a history of allergy.

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Anesthesia in a patient with multiple drug allergies

Risk factors for immediate hypersensitivity to anesthetic drugs

It is well-established that the main risk factor for a perioperative immediate hypersensitivity reaction (IHR) is a previous, uninvestigated IHR. However, providers should be aware that previous tolerance to a drug does not exclude future IgE-mediated reactions to the same drug. The major determinant of an IHR to a drug is the chemical structure along with multiple genetic factors of the patient [51]. Patients with previous reactions should undergo allergological assessment prior to undergoing anesthesia when possible [20].

Patients often report multiple drug allergies. Whether these are true hypersensitivity reactions or intolerances often remains in question. Definitions have been put in place to categorize patients with multiple drug allergies. MDA syndrome is defined as a hypersensitivity reaction to two or more drug classes. The prevalence of this syndrome is unknown and most often presents with urticaria and/or angioedema [52]. This is likely due to cross-reactivity to similar epitopes on allergens that are recognized by the IgE antibody [20]. This cross reactivity has been seen in neuromuscular blocking agents, antibiotics, iodinated contrast agents, and certain foods.

Neuromuscular blocking agents (NMBA)

NMBAs are regularly used during anesthesia and are one of the most common causes of perioperative anaphylaxis. They are estimated to be responsible for 50%–70% of perioperative hypersensitivity reactions.

Reactions are thought to be secondary to an IgE-mediated mechanism, which would suggest preformed IgE antibodies from a previous exposure. However, it has been noted that up to 75% of reactions have happened on first exposure, indicating cross-reaction with IgE generated from exposure to an unrelated substance [53]. Studies have shown that the substituted ammonium groups on NMBA are the structural allergenic determinants. Tertiary and quaternary ammonium groups are common in the environment, including drugs, cosmetics, foods, and more. Previous exposure to these substances is a possible, however, unproven mechanism of cross-reactivity with NMBA [33]. There has been interest in a study demonstrating increased incidence of anaphylaxis to NMBAs in Norwegian patients exposed to pholcodine compared to Swedish patients who were not exposed to pholcodine. This was due to the availability of pholcodine-containing cough syrup in Norway but not Sweden. The hypothesis is pholcodine exposure leads to sensitization to NBMA and other quaternary ammonium ions. Otherwise, alternatively increases the titer of IgE, thus increasing the risk of an allergic reaction. Another prevalence study that supported this claim, however, simultaneously demonstrated that other unknown substances are likely involved in the sensitization to NMBA [53]. Nonetheless, this study did illustrate the likely ability of an unrelated substance to sensitize patients to NMBA. The only risk factor for a reaction to an NMBA is a previous undocumented IHR during anesthesia involving NMBA. If a hypersensitivity reaction has occurred further allergological workup should be undertaken. Multiple NMBA should be tested as negative skin tested NMBA have been safely used in patients with previous reactions to other NMBA.

Food allergies and propofol

Propofol is commonly used for the induction and maintenance of anesthesia and sedation in the ICU. Propofol is dispensed as an emulsion containing soybean oil, egg lecithin, and glycerol. Allergic reactions to propofol are rare with a past estimated incidence of 1:60,000 exposures [54]. However, given the contents of the propofol emulsion, there has been concern in the past of its use in egg, soy, and in patients with peanut allergy. Often leading the provider to avoid its use in these patients. The question is, does the evidence support the avoidance of propofol?

Egg allergies are common in children with an estimated prevalence of 2%. However, they are often outgrown by adulthood. The reaction is typically to proteins in the egg whites, such as ovalbumin, ovomucoid, or conalbumin. Lecithin, a component of propofol, is a purified phosphatide that is found in

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the egg yolk and is not the allergic determinant. The 2-isopropyl or phenol groups are thought to act as the allergic determinant that binds IgE antibodies [54]. To date, there is a lack of definitive evidence supporting the connection between allergic reactions to propofol in patients with egg allergy. In the past, recommendations have varied about propofol use in patients with egg allergy ranging from avoiding its use in all patients, only avoid use in patients with anaphylactic reactions, or avoidance is unnecessary. There are no consensus guidelines on the administration of propofol in patients with egg allergy; however, several recommendations exist. For example, the childhood Allergy Committee of the Spanish Society of Allergy and Clinical Immunology recommends that: 1) Patients with an anaphylactic reaction to eggs either receive an alternate anesthetic or a small test dose of propofol to assess for response. 2) there is no contraindication in patients with nonanaphylactic reactions to eggs [55]. Given the available evidence, it is not necessary to avoid propofol use in patients with egg allergy. However, if a patient has a known anaphylactic reaction to eggs, it is reasonable to consider using another anesthetic or administering a small test dose and assessing patients' toleration.

Soy allergy is one of the more common food allergies among children with an estimated prevalence of 0.4%. Most patients develop tolerance in late childhood and the prevalence in adults remains less than 1%. The major allergens in soy are proteins belonging to the cupin family such as glycinin and beta-conglycinin. Anaphylactic reactions to soy are rare [51]. The soybean oil found in propofol is highly refined and is unlikely to have any significant concentration of allergenic proteins. Therefore, it is highly unlikely that propofol would elicit a hypersensitivity reaction in a patient with soy allergy [3]. Given these facts, there is no reason to withhold propofol in patients with soy allergy.

Peanut allergy is another common food allergy among children and prevalence is increasing. There has been a 3.5-fold increase in peanut allergy in the past decade. Peanut allergies tend to be lifelong and reactions can range from mild to severe [56]. The concern for propofol use in these patients is due to the cross-reactivity of peanuts and soy, as they are both in the legume family. As previously mentioned, there is currently not enough evidence to avoid propofol use in patients with soy allergy. Likewise, there is no need for avoidance in patients with peanut allergy.

Allergies to contrast agents

Iodinated contrast agents consist of solutions of tri-iodinated benzene rings and are commonly used in diagnostic and surgical procedures. It is used in over 75 million procedures worldwide each year and is recognized as one of the more common causes of hypersensitivity reactions [57]. The exact allergic determinant remains unknown as the iodine atom is not felt to be the source [3]. An IgE-mediated mechanism is the suspected cause. This is supported by evidence including positive skin tests, detection of contrast-specific IgE in patients with past reactions, positive basophil activation test in a subgroup of patients, and high levels of tryptase during severe reactions. However, no prior sensitization phase is required for a patient to experience a reaction. This has led to possible alternative explanations such as a direct membrane effect due to the osmolality of the solution leading to the activation of the compliment system and bradykinin formation. However, this has not been proven.

The incidence has been reported as 0.7%–3% of administrations, with severe reactions at 0.02%–0.04% and fatal reactions at 0.00001%–0.0003% of contrast administrations [57]. The major risk factor for a hypersensitivity reaction to contrast media is a previous reaction. Other possible risk factors include female gender, renal insufficiency, asthma, drug allergies, food allergies, contact allergies, and IL-2 treatment; however, these are less prominent predisposing factors. IHRs to contrast agents occur rapidly after administration, usually within 5 min, with 96% occurring within 20 min. The most common signs are pruritus, urticaria, and angioedema occurring in about 70% of reactions. Heat sensation, nausea, and vomiting can also occur, including more severe symptoms such as dyspnea, bronchospasm, tachycardia, and hypotension.

Following a reaction, further allergological workup should be pursued such as skin prick testing. Cross-reactivity between different radiocontrast medias is common, so several different solutions should be tested in an attempt to find a contrast dye that is safe for the patient [57]. Patients have successfully received alternate contrast dyes, which tested negative on skin prick testing following a previous reaction [3] (See Table 2).

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Table 2
Methods of Allergy Assessment. Information adapted from [58,59].

Methods of Allergy Assessment	Description
Skin prick testing (SPT)	Dilute solution of allergen introduced into the skin with a skin prick device. If IgE is present, a wheal reaction occurs. Reaction sizes are compared to positive and negative controls.
Intradermal test	Dilute solution of allergen injected into dermis. More sensitive than SPT for when attempting to avoid false negatives.
Allergen-Specific IgE testing	Blood drawn from patient. Serum is exposed to allergens. IgE detected by enzyme-conjugated anti-IgE causing changes in color or fluorescence.
Basophil activation test	Historically performed by measuring mediators in blood released from response to an allergen (i.e., histamine and leukotrienes). Recent techniques use flow cytometry to measure markers on the surface of basophils.

Seafood allergy and protamine

Allergies to seafood consist of two distinct groups, fish and shellfish. The major allergenic protein in fish is parvalbumin, while in shellfish it is tropomyosins. There is no cross-reactivity between fish and shellfish. These two allergens are among the most common food allergies to provoke anaphylaxis [3]. Protamine is an alkaline polypeptide originally produced from the sperm of salmon. It is used to reverse the effects of heparin and can be found complexed with insulin, such as neutral protamine Hagedorn (NPH). While hypersensitivity reactions to protamine are rare, and evidence is lacking, two possible risk factors are fish allergy and NPH insulin use. Studies have evaluated the incidence of protamine reactions in patients using NPH insulin. The incidence was noted to be 0.6% compared to 0.06% in other cardiac patients. However, no evidence was found for a protamine allergy [51]. Additionally, there have been no cases of reactions to protamine in patients with fish allergy, nor has cross-reactivity been identified between salmon and protamine in patients who have had allergic reactions following ingestion of salmon [3]. Given the evidence, there is no reason to avoid using protamine in patients with fish allergy or patients using NPH insulin.

Prevention of allergic reactions in anesthetized patients

The strongest preventative measure of IHRs is performing a detailed preoperative evaluation and obtaining a thorough history of prior allergies. Prior to surgery, it is important for the anesthesiologist to gather any clinical or past medical history, particularly those involving medications and latex. The most common culprits involved in perioperative IHRs include but are not limited to medications, antibiotics, and latex. It is also important to gather patient history of allergies to food or any other specific allergen, which may suggest cross-reactivity and may require a change in anesthetic management.

Prophylactic treatments with corticosteroids alone or in combination with H1 antagonist have provided some benefit in clinical practice, but remain a matter of debate. Premedication does not prevent a hypersensitivity reaction but rather delays the response or mitigates the events involved in a hypersensitivity reaction. The effect is dependent on the type of hypersensitivity response or the length of exposure to allergen. However, there is no evidence that pretreatment can effectively prevent the onset or reduce the severity and could possibly delay the reaction, making it more difficult to recognize early signs of anaphylaxis [13].

After gathering a detailed history on the patient, the most effective management to prevent IHR is to avoid the allergen itself, whether it is a medication or latex, or even to avoid medications in the same class. If it is absolutely essential, when a patient is to have a specific medication, then the graded approach is recommended. Although, be aware that subsequent exposure to a known culprit agent may

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cause a greater response, potentially a life-threatening reaction. Also, it is important to appropriately time the administration of medications or antibiotics to allow time to detect possible anaphylaxis [60] (See Table 3).

NMBAs

The most common cause of perioperative anaphylaxis in many studies to date is NMBAs. The tertiary or quaternary ammonium group is suspected to be the culprit, and is common in all medications in this class. This common group leads to a high likelihood of cross-reactivity. Local anesthetics, regional anesthesia, or inhaled anesthetics are effective alternatives. When it is mandatory to administer an NMBA in a patient with a previous allergy to a drug in this class, an incremental challenge with an NMBA different from that, which elicited the reaction, should be used [13].

Antibiotics

The second most common culprit of perioperative IHR is penicillin, particularly those containing beta-lactam rings. However, most reported penicillin reactions are not associated with immunoglobulin E mediated reactions but rather due to decrease in penicillin-specific antibodies over time [61]. Given the similar molecular structure between penicillins and cephalosporins, it is recommended to not use cephalosporins. However, it has been suggested that the potential of cross-reactivity between penicillins is related to similarities in R1 side chains rather than the beta-lactam ring. If a patient has a history of IHR to penicillins, the best choice is to find an alternative antibiotic without penicillin-like characteristics or molecular structure. It would be useful to separate the administration of prophylactic antibiotic therapy and anesthetic induction to identify and treat the reaction as early as possible [14].

Latex

The third most reported culprit of perioperative anaphylaxis involves latex, which remains a serious problem for sensitized patients. Most hospitals have taken serious measures to reduce the risk of exposure to latex, but it is important to be vigilant as there are still possibilities for exposure. Screening questionnaires are effective in identifying patients with latex allergy or a possibility of it, likely preventing perioperative complications. Equally important is information about reactions to bananas, avocados, kiwis, and other fruits such as pineapples because of the described cross allergies [62]. For this reason, it is important for hospitals to designate a latex-free room for patients who are at a high risk, particularly those with a history of Grade 3 or 4 anaphylactic reactions. If such a room is not available, then the case should be posted as the first case in a sanitized room and latex products should

Table 3
Prevention of allergic reactions I anesthetized agents.

Offending Agent	Preventative measures
NMBAs	• Local anesthesia without need for deep sedation • Incremental challenge
Antibiotics	• Use of alternative antibiotic without penicillin like characteristics or similar molecular structure
Latex	• Avoidance of latex use • Latex-free rooms • Examine all products for possible latex such as IVFs, medication vials, and catheters.
Radio contrast Materials	• Premedication protocol with corticosteroids and antihistamines
Others	• CHG or iodine can be interchanged • Avoid colloids if patient has prior allergy ◦ Dextran 1 can be used for those allergic to dextrans • Wash PRBCs for patients with IgA deficiency

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be removed on the previous day. Also, be mindful of latex in medication vials, IVF bags, or even catheters as it may be missed.

Radiographic contrast material

Hypersensitivity reactions to contrast media have been noted and continue to rise due to the increasing use in modern medicine. The pathophysiology is not completely understood, but there is strong evidence these reactions are T cell mediated. With this evidence, there has been the development of premedication protocols to be used in patients with IHR to contrast agents that require certain imaging or procedures utilizing contrast media. Several possible premedication protocols have been proposed, with a protocol using a combination of H1-antihistamine (e.g., 1 mg/kg diphenhydramine 1 h before application) and several doses of corticosteroids (e.g., 50 mg prednisone 13, 7, and 1 h before application) [63]. Although this has prevented IHR in some patients, it cannot reliably be used to completely avoid reactions, instead it has helped to reduce the severity. If dyes are essential in a patient with previous reactions, future administration should involve either using a smaller amount of dye or using a different dye such as methylene blue, indocyanine green, or technetium. If possible, it is best to use another imaging modality rather than expose the patient to contrast media altogether.

Other culprits

Caution should be taken in patients with IgA deficiency as blood products could cause reactions if RBCs are not washed. In patients with a history of IHR to chlorhexidine (CHG), povidone iodine is an acceptable alternative. Although many have had minimal reactions to CHG, it is increasingly significant during catheter placement because CHG is invaginated in the blood circulation. Colloids also have a tendency to cause allergies, particularly gelatin solutions. If a patient has a history of allergy to dextrans, dextran 1, a hapten inhibitor can be given to reduce the risk of life-threatening IHR.

Clinical considerations for patients with multiple drug allergies presenting for surgery under general anesthesia

There are many drugs utilized by anesthesiologists throughout an operative case with the potential to induce hypersensitivity reactions: antibiotics, neuromuscular blocking agents, induction agents, opioids, etc. Patients with known MDA or suspected drug allergies may benefit from an allergological assessment, such as skin prick and intradermal testing, before operative intervention to confirm their susceptibilities and plot the course of anesthetic management [64–67].

The most common causes of anaphylaxis were NMBAs accounting for 58%–62%, latex for 16% and antibiotics for 15.1% of cases [68,69]. Cross-reactivity is also common for the benzylisoquinolinium group of muscle relaxants as this group of drugs share a quaternary ammonium group [68]. It should be noted, however, that the term “anaphylaxis reaction” is usually reserved for IgE-mediated Type I hypersensitivity reaction. While in many cases clinically indistinguishable, “anaphylactoid reaction” refers to the clinical picture Rajan et al [64] created by histamine release through other mechanisms such as through a direct chemical effect without prior sensitization [69,70]. Serum tryptase can also be used to help differentiate between the two: levels <15 ng/mL is suggestive of anaphylactoid/mild anaphylaxis and levels >20 ng/mL confirms anaphylaxis; a ratio of reaction to baseline tryptase >2 is also suggestive of anaphylaxis (TDR/BT > 2) [64]. However, the use of tryptase to distinguish between chemical and immune reactions has been the source of debate [71].

In a case series, Rajan et al. reports on six patients who had positive intradermal skin test for almost all the commonly used anesthetic agents. Of the six, four were sensitive to fentanyl, two were sensitive to acetaminophen, and one was sensitive to antihistamines. Of note, all were sensitive to propofol, ketamine, morphine, atracurium, vecuronium, lidocaine, and bupivacaine [64]. On the day of surgery, patients who were allergic were premedicated with acetaminophen 1 g one h prior to operation. In the operating room, patients were placed on EKG, BP, and pulse oximeter monitors and were given IV hydrocortisone 100 mg and dexamethasone 8 mg to reduce the risk of anaphylaxis and for antiemetic effects. Those who were not allergic to fentanyl received 10 μg intravenously slowly. Sevoflurane 8% in

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oxygen was used for induction with a gas flow rate of 6 L/min until the loss of consciousness. Nitrous oxide (50%) was added and bag ventilation until apnea, followed by intubation through direct laryngoscopy. One case did develop hypotension, which was managed with adrenaline bolus. Maintenance was achieved with sevoflurane. Breathing attempts were circumscribed with temporary hyperventilation and increase in sevoflurane concentration. No patients developed any skin manifestations during the procedure. All patients had an unremarkable postoperative period from anesthesia standpoint except for one who developed postoperative nausea and received 4 mg ondansetron intravenously because she was not allergic per allergy testing. However, soon after drug administration, she developed urticarial lesions all over the body with hypotension and wheezing, which required a 200 μg adrenaline bolus and infusion for 4 days postoperatively; whenever infusion was stopped, urticarial lesions reappeared although there was no hypotension or wheezing after the initial bolus [64].

Sevoflurane was used as there have been no reports of anaphylaxis (Type I hypersensitivity) related to volatile inhalation anesthetic, halothane, enflurane, and isoflurane but may be associated with immune-mediated hepatic injury (Type II or Type III hypersensitivity) [64] Terada et al. and Nakamura et al. also report successfully using primarily inhalation anesthetics (sevoflurane and nitrous oxide) for induction and maintenance of anesthesia for their patients with a history of MDA despite not performing allergological skin tests [72,73]. The use of inhalation anesthesia in patients with MDA is a relatively safe course of action.

Another possibility would have been to use regional anesthesia. Kulkarni et al. reports on a patient with MDA managed with a T8-9 thoracic epidural achieving T4 to L1 sensory block for a laparoscopic cholecystectomy. Intraoperative hemodynamics remained stable and postoperative analgesia was managed using fentanyl patch and oral Ibuprofen. The patient was discharged uneventfully after 48 h [15]. Daszkiewicz et al. also report a patient needing cholecystectomy who was managed with regional anesthesia. The patient was allergic to atropine, midazolam, etomidate, fentanyl, tramadol, suxamethonium, vecuronium, cisatracurium, and metamizole. They ruled out lidocaine and bupivacaine sensitivity and used combined spinal-epidural (CSE) anesthesia to achieve a T2-L1 block. Surgical conditions were comfortable for the surgeons and patient and the postoperative period was uneventful [74]. Surgical conditions were comfortable for the surgeons and patients with uneventful postoperative period [74].

Other case reports of anesthetic management of patients with MDA involved using fewer common alternatives that the patient was not sensitive to. An early case report of a myelodysplastic child by Sethna et al. with a history of intraoperative anaphylaxis eventually determined sensitivity to succinylcholine, methohexital, pancuronium, penicillins, and latex. Management with thiopental, nitrous oxide, halothane, vecuronium, gentamicin, and vancomycin was finally uneventful [75]. A patient with a history of serious intraoperative anaphylaxis to NSAIDs (Loxonin and Niflan), antibiotics (Kefral and Minomycin), succinylcholine, and vecuronium, reported by Horiguchi et al. did well with regional anesthesia with diazepam, nitrous oxide, and sevoflurane [76].

Taken together, these case reports suggest patients with MDA can benefit from allergological assessments before operative intervention to allow the clinician to tailor the best anesthetic regimen. In cases where this is not possible, consider regional anesthesia or default to inhalational anesthesia for induction and maintenance.

Summary

In the perioperative care of patients, MDA should be taken into serious consideration, although the occurrence rate overall is low. Unlike cross-reactivity, patients with MDA usually demonstrate allergic reactions to non-cross-reacting drugs. Although the mechanisms of development of MDA is not fully understood, IgE-mediated activation of mast cells and basophils is regarded to play an important role. It has also been suggested that a certain group of CD4+ T cells is critical in reducing the threshold for activation by drugs. Patients with MDA are at high risk during anesthesia. Therefore, before the administration of anesthesia, patients' history of allergy should be thoroughly inquired through both interview and chart review. Noticeably, many self-reported drug allergies are incorrect. In some cases, patients may develop very similar reactions to multiple unrelated drugs, this is when psychological conditioning should be considered. To avoid misinterpretation of patients' allergy history, tests of the

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anesthesia agents should be given intradermally and/or intramuscularly. When necessary, in vitro tests may be considered, such as solid phase immunoassay of drug-specific IgE and flow cytometry measuring drug-induced basophil activation. Anesthesia agents and other medications should be carefully selected for patients with history of MDA. This is because agents including but not limited to NMBAs, contrast dyes, local anesthesia, latex, beta-lactam, and NSAIDs all have high allergic potential in sensitive patients. An alternative method to protect anesthetized patients at high risk, anesthesiologists to employ general anesthesia (e.g., epidural) in patients who qualify. Overall, satisfactory prevention of allergic reactions in anesthesia is very difficult to reach, partly because many patients do not have previous allergy history. To protect anesthetized patients at high risk, anesthesiologists often administer antihistamines or corticosteroids before anesthesia. However, there is lack of evidence to support the prophylactic use of antihistamine and corticosteroid. Ideally, patients at high risk should undergo a thorough investigation for the offending agent(s), and that agent in addition to the cross-reacting drugs should be avoided in anesthesia. When allergic reaction, particularly the life-threatening anaphylaxis occurs in the perioperation process, the potential offending agent should be discontinued immediately. The administration of epinephrine with possible repeated bolus and 100% oxygen are the first-line treatment. Intubation may be necessary if the patient's airway is not secured. Antihistamines and corticosteroids may also be administrated depending on the patient's condition. In general, allergic reactions including anaphylaxis in anesthetized patients may cause catastrophic outcomes. The prevention and management of these situations is a critical yet challenging task that requires close collaboration between anesthesiologists, surgeons, and allergists.

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Practice points

- In the evaluation of patients undergoing anesthesia, providers will encounter a broad range of pathologies often requiring multiple pharmacological treatments.
- As the anesthetic plan itself will most often involve multiple classes of medications, a unique challenge is presented in the patient with multiple drug allergies.
- Adverse drug reactions are recognized as one of the most common causes of morbidity and mortality in anesthesia.
- Therefore, an understanding of the mechanisms and common triggers is important for the prevention, recognition, and treatment of allergic reactions.

Research agenda

- A careful clinical history proves to be critical in preventing perioperative hypersensitivity reactions to prevent exposure to the offending agent.
- This is of paramount importance to avoid further hypersensitivity reactions because they cannot effectively be prevented by premedication.
- There is no protocol or premedication that can completely prevent these reactions; therefore, it is important to gather a thorough history and to be vigilant to identify an IHR as it is often noticed late in the perioperative phase.

Declaration of Competing interest

None.

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